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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/813,829	03/06/1997	BRIGID L. M. HOGAN	16016.0005	3939
23859	7590	03/23/2006	EXAMINER	
NEEDLE & ROSENBERG, P.C. SUITE 1000 999 PEACHTREE STREET ATLANTA, GA 30309-3915			WOITACH, JOSEPH T	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 03/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/813,829

Applicant(s)

HOGAN, BRIGID L. M.

Examiner

Joseph T. Voitach

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/18/2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4 and 37-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4 and 37-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 March 1997 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application filed March 6, 1997, is a continuation of 08/217,921, filed March 25, 1994, now US Patent 5,690,926, which is a continuation in part of 07/958,562, filed October 8, 1992, now US Patent 5,453,357.

Claims 1-3, 5-36 have been canceled. Claims 4, 37-44 are pending and currently under examination.

Response to Amendment

The declaration of James Kelly filed under 37 CFR 1.132 filed November 18, 2005 is insufficient to overcome the rejection of claims 4, 37-44 based upon 35 USC 112, first paragraph, as set forth in the last Office action. Dr. Kelly's summary of the disclosure of '829 is noted, however the conclusion that pluripotent stem cells (claim 4) were isolated, in particular embryonic stem cells (claims 37-44) is not consistent with the source of material used in the isolation methods. The methods disclosed in '829 use primordial germ cells and fetal gonads (see specification starting on page 23). While it may be that these cells that were isolated were AP positive, as well as SSEA1, TRA 1-60 and -80, this is insufficient evidence to conclude that the cells are embryonic stem cells. At the time of filing, it was accepted that EG cells are isolated from the gonadal ridge, not embryonic stem cells. Embryonic stem cells are isolated from the ICM of early stage embryos. With respect to the written description rejection, it is maintained that while certain cell types may share common cell surface markers, in the instant case, this is

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insufficient to uniquely define a cell type since the markers are shared by a variety of other cell types.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 4, 37-44 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 15, 18-21, 23-28 of copending Application No. 10/327,400.

Applicant indicates that a terminal disclaimer will be filed. See page 4 of Applicant's amendment.

Applicant's willingness to file a terminal disclaimer is noted, however one has not been received by the office.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This is a new rejection, made under 35 USC, first paragraph, enablement.

Claims 4, 37-44 are to a composition comprising human feeder cell and an isolated human pluripotent ES cells which can be maintained on feeder layers for at least 20 passages and give rise to EB's and multiple differentiated cell phenotypes on monolayer culture; a composition comprising human feeder cell and an isolated human pluripotent ES cells which can be maintained on feeder layers for at least 20 passages and give rise to EB's and multiple differentiated cell phenotypes on monolayer culture. The claims are not enabled as the composition and isolated human ES cells have no enabled use.

The specification discloses the claimed murine and human pluripotent embryonic stem cells of the composition and the claimed cells to be used in the production of transgenic animals by injecting the ES cells into a blastocyst and growing the blastocyst in a foster mother, aggregating the ES cell with a nonhuman morula stage embryo to produce chimeras, which subsequently can be mated to obtain germline transmission of ES cell traits (specification, page 13, lines 26-32). However, the art has it clear that only mouse ES cells have the ability to colonize the germ line and pass ES cell traits to progeny. Bradley (1992) states there are several reports of ES cells from farm animals, in particular sheep and pigs, but they have not been shown to contribute to somatic tissues or germ cells (Bradley et al. (1992). Gardner (1997) states that

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only in mice are ES cells known that form gametes after injection of the ES cells into embryos (Gardner et al. (1997) *Int. J. Devel. Biol.* 41, 235-243). Moreadith (1997) states several putative ES cells lines had been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, but Moreadith also states that the technology in was limited to mice (page 214, col. 1, parag. 3, lines 5-12). Prella (1999) states many embryo-derived cell lines resemble morphologically mouse ES cells, and have the ability to differentiate in vitro, but there is no evidence of live born, fertile germ line chimeras in mammalian species other than mouse (page 222, col. 2, parag. 1, lines 10-16). Wheeler's (2001) teaches putative pig ES cells, which produced two-pig chimera but there is no disclosure that the chimera gave rise to a pig of the ES cell phenotype (pages 1351-1352). Further, Wheeler states, in reference to ES cells recently isolated and the production of swine and cattle chimera, "validation of totipotency of these embryo-derived ES cell lines awaits conformation" (page 1351, paragraph. 1, last sentence). Niemann (2005) state very simply "true ES cells (that is those able to contribute to the germ line) are currently only available from inbred mouse strains" and further states that ES-like cells have been reported for several farm animal species without evidence of germ line transmission in chimeras produced using them (Niemann, page 290-291, bridging sent and page 291, lines 5-9). Thus, from the time of applicant's earliest priority date to the time of filing the present application, only mouse ES cells are available for the production of animals having an ES cell trait. The claimed composition and cells, therefore, have no enabled use in the production of chimera that in turn can be used to produce an animal have a phenotype or genotype of a non-mouse ES cell.

Further, there is no enabled use of the claimed invention as providing cells for therapeutic purposes. The specification states derivative of human ES cells could be placed in the brain to treat neurodegenerative diseases (page 14, lines 6-7). The implantation of daughter ES cells to treat any disease is not enabled. Mouse inner cell mass cells were known at the time of filing to lose their totipotency at the expanded blastocyst stage (Cruz, page 150-151). Further, EG cells can undergo spontaneous differentiation but may be unable to support normal development due to epigenetic modifications, which have occurred during formation of the primordial germ ridge (Eiges, page 529, col. 2, paragraph. 2, lines 7-10). The specification does not provide guidance for the implantation of human cells produced by the disclosed method in the treatment of neurodegenerative disease or any disease because the ability of an ES cell to develop in situ into a differentiated cell is in question because of the loss of totipotency or pluripotency past the blastocyst state of development. The specification teaches the use of PGC's, cells that are past the blastocyst stage and are partially differentiated to become germ cells, as a source of PGC's. There is no evidence that these cells can be reprogrammed in vitro to support development of any tissue type. The claimed composition and pluripotential mammalian and human ES cells are not enabled for a therapeutic use. The specification does not provide any evidence that these compositions or cells could overcome the unpredictabilities known in the art at the time of filing.

There is doubt as to whether the methods disclosed to produce pluripotent mouse ES cells would produce non-murine pluripotent ES cells, and in particular would produce human pluripotent ES cells. The specification states the development of mouse ES cells by culture of mouse PGC's in the presence of bFGF, SF and LIF permits PGC's continue to proliferate in culture to give rise of colonies of ES cells (page 3, lines 15-17). The specification provides

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guidance for the production of mouse pluripotent ES cells from mouse PGC's in culture.

Evidence that the methods disclosed would not result in non-murine or human ES cells comes from data regarding cell markers and culture conditions. Further, there is no evidence that applicant's cultured PGC's, referred to in the art as EG cells, are actually ES cells, which, according the art, are cultured inner cell mass cells (Carpenter, page 80, col. 1, parag. 2, lines 12-19). The specification fails to provide guidance on the production of non-murine or human pluripotent ES cells.

With regard to cell markers, the specification teaches cultured mouse PGC's exhibit both alkaline phosphatase staining and SSEA-1 staining (specification, page 16, line 20 to page 17, line 2). Mouse ES cells express SSEA-1, but not SSEA-3 or SSEA-4, as a cell surface marker (specification, page and Laslett, page 298, col. 2, lines 1-6). Human ES cells, it should be noted, do not express SSEA-1, but do express SSEA-3 and SSEA-4 (Laslett, page 298, lines 6-13). Human EG cells, which are cultured PGC's, express SSEA-1, SSEA-3 and SSEA-4 (Laslett, page 298, col. 2, lines 14-16). ES cells isolated produced from the inner cell mass cells of rhesus monkey embryos, showed the same cell marker pattern as human ES cells: positive for alkaline phosphate, SSEA-2, SSEA-4 (Thomson (1995), page 7845, col. 2, parag. 2, lines 7-10). Again human and rhesus monkey ES cells are in contrast to mouse ES cells that express SSEA-1, but not SSEA-3 or SSEA-4. An artisan following the would not have produced human or rhesus monkey ES cells, but would have produced human EG cells, which express SSEA-1 (Shamblott, page 13729, col. 2, parag. 3, lines 1-4). Shamblott states that this difference in SSEA-1 marker expression between rhesus monkey and human EC cells may indicate the human PGC-derived cultures, such as applicant's, are differentiated (Shamblott, page 13729, col. 2, parag. 3 lines 5-

8). Shambloott also states the SSEA-1 differences may reflect morphological differences between human EC and rhesus ES cells (Shambloott, page 13729, col. 2, parag. 3, lines 10-14). The differences in cell marker sets between human and rhesus monkey ES cells and human EG cells, as would be produced by the claimed method, teach that the skilled artisan following the present disclosure would not have made non-murine or human ES cells, but non-murine or human EG cells. The specification does not provide evidence that the marker pattern of the human embryonic cells obtained using the disclosed method reflects that of human ES cells as opposed to human EG cells (see Thomson (1998) and Shambloott, above). Thus, there is reason to doubt that the method disclosed enables the production of pluripotent non-murine or human ES cells.

Moreover, the culture requirements disclosed for mouse PGC's to become ES cells does not parallel that of human ES cells. For example, human ES cells are not refractive to LIF. Mouse ES cells produced by culture of mouse PGC's requires SF (membrane associated and soluble), bFGF and LIF (specification page and Laslett, page. 296, col. 2, lines 1-5). Human ES cells only require a feeder layer (Thomson (1998), page 1146, col. 1, parag. 2, lines 12-17). Further, both rhesus and human ES cells are grown in media containing 20% fetal calf serum (Thomson (1995), page 7844, col. 2, parag. 2, lines 9-12) and Thomson (1998), page 1147, col. 2, fn. 6, lines 10-15). The specification discloses 15% fetal bovine serum (specification, page 16, line 3). Thus, the culture conditions taught by the specification are not those, which lead to the isolation of human ES cells. One following the methodology of the specification would not have produced non-murine or human pluripotential ES cells.

Lastly, the specification discloses the use of the non-murine pluripotent ES cells to screen for factors to determine which factors produce more derivative or more differentiated cells.

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However, this is not enabled because the method disclosed would not produce non-murine pluripotent ES cells for the reasons set forth above. Any results obtained would not be reflective ES cell requirements.

Thus, for the reasons presented above the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to implement the claimed invention.

Claims 4, 37-44 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants summarize the requirements of written description (pages 4-7) and argue that the instant claims and disclosure meet the requirements of 35 USC 112, first paragraph, and have provided a declaration supporting that the claimed product has been reduced to practice (pages 7-8, and supporting declaration-discussed above). Applicant's arguments have been fully considered, but not found persuasive.

As noted previously, the specification teaches and the claims specifically set forth a series of histological markers the claimed human stem cell comprises, however the specification fails to provide evidence that these markers are specific for human and post-filing art clearly teaches that certain markers are clearly not present on human stem cells. Further, beyond the differences in histological markers the ability to isolate and maintain a human stem cells has been demonstrated to be different from that used in isolating and maintaining mouse stem cells,

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for example in the ability of the isolated cell to respond to LIF in culture. In this case, it appears that Applicant is relying in part on the definition of an embryonic stem cell, and the correlation with the mouse embryonic stem cell that was known at the time of filing. It has been accepted that the specification appears to provide methodology to isolate stem cells in general, however the specification fails to adequately describe the human cell that is isolated by that methodology. While possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention, the present specification only provides for embryonic germ cells isolated from humans. In this case, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Voitach

Joe Voitach
AUG 30